REMARKS

Amendments to the Claims

Claims 4, 12 and 43 have been amended herein.

Applicants have amended claim 4 to delete the limitation in (ii) which recites hybridization to "full-length SEQ ID NO: 5," and add a functional limitation directed to a polypeptide, "wherein said polypeptide specifically binds to an antibody directed toward a von Willebrand Factor type A domain." Support for this amendment can be found in the specification at Example 5, original claim 34, and in paragraphs [0088], [0090], and [0091].

Further, Applicants have amended claim 12 to delete language which refers to a von Willebrand Factor A-Related Peptide.

Applicants note that claim 12 was previously amended in our response filed on March 21, 2007, but such amendment was not noted in the Listing of Claims. Applicants apologize for this error and supplement the amended format herein. Claim 12 should have read:

12. (Currently Amended) An~~The~~ isolated polypeptide ~~of Claim 4,~~ comprising a von Willebrand Factor A-Related Protein having an amino acid sequence set forth in SEQ ID NO:6.

Also, Applicants replaced language in claim 43 (i) and (ii) requiring 95% and 99% "similarity" to SEQ ID NO: 5, with "identity," and corrected the article from "the" to "a" in the preamble. Support for this amendment is found in Example 10, paragraph [0142] of the specification. Finally, Applicants added a functional limitation to claim 43 directed to an isolated polypeptide, "wherein said polypeptide specifically binds to an antibody directed toward a von Willebrand Factor type A domain." Support for this amendment can be found in the specification at Example 5, original claim 34, and in paragraphs [0088], [0090], and [0091].

None of these amendments introduces new matter.

Amendments to the Specification

Applicants have amended paragraph [0153] of the specification to reintroduce language originally filed, but deleted in the amendment filed on October 2, 2006.

Amended paragraph [0153] now reads:

[0153] A human homolog of murine WARP was identified by database homology searching. ~~The nucleotide~~ Nucleotide sequence (SEQ ID NO: 5) ~~and corresponding~~ corresponds to amino acid sequence (SEQ ID NO:6).

No new matter is introduced by way of this amendment because this language appeared in the specification as originally filed; its entry is respectfully requested.

Objections to the Disclosure

The objection to the amendment filed October 2, 2007 under 35 U.S.C. 132 for introducing new matter into the disclosure is respectfully traversed. Applicants submit that the substitute sequence listing corrected an error in the specification as filed, and no new matter was being introduced.

In the March 31, 2006 office action, the Examiner contended that there was no common structural relationship between the nucleotide of SEQ ID NO:5 and the polypeptide of SEQ ID NO:6, stating that SEQ ID NO:5 is missing a codon corresponding to the Asp amino acid of SEQ ID NO:6 at position 211. Applicants once again thank the Examiner for bringing this error to their attention.

In the amendment filed October 2, 2007, Applicants acknowledged this missing codon and reserved their right to address the correction at a future time. In the later response to the Notice of Panel Decision dated October 31, 2007, Applicants submitted a corrected sequence listing with the codon GAY, at nucleotide position 631 (spanning from nucleotides 631-633) to correct the structural relationship between the nucleotide of SEQ ID NO: 5 and the polypeptide of SEQ ID NO: 6. As corrected, the codon GAY codes for Asp at position 211 of SEQ ID NO:6.

GAY can represent both GAT or GAC ("Y" representing either pyrimidine, T or C)[1], which both code for Asp and which are the only two codons which encode Asp.

In the present office action, the Examiner argues that introduction of the GAY codon represents a departure from the specification and claims as originally filed, and that Applicants relied on Figure 6 for support, which was never filed with the original application. The Examiner also argues that if there was a Figure 6 filed, the Figure would have provided for either GAT or GAC but not GAY. Applicants respectfully traverse this objection.

Applicants apologize for referring to Figure 6 in our last response because Figure 6 never existed. However, since Figure 6 never existed, the Examiner's speculation as to what would have shown holds no merit. Rather, SEQ ID NO:5 and 6 as present in the originally filed application, together with the specification, provide support for the correction made in the substitute sequence listing.

The codon GAY appears in the substitute sequence listing and conforms to the requirements of MPEP 2422. The omission in SEQ ID NO:5 of this codon is a clear and obvious error, because SEQ ID NO:5, uncorrected, would not encode the amino acid sequence of SEQ ID NO:6. That SEQ ID NO:5 encodes SEQ ID NO:6 is supported by the instant specification, for example paragraph [0071] of the originally filed specification at page 28, which states "[t]he cDNA sequence encoding WARP and its corresponding amino acid sequence are represented in SEQ ID NO:5 and 6, respectively." In order for SEQ ID NO:5 to encode SEQ ID NO:6, the codon encoding ^{211}Asp must be inserted. This does not constitute new matter, because the above-quoted statement and SEQ ID NO:6 provide support for the insertion of the codon encoding ^{211}Asp. As the only two codons encoding Asp are GAC and GAT, the inserted codon GAY is an accurate representation of both alternatives. If the Examiner prefers, the inserted codon could be listed as YYY, where it is indicated that YYY encodes Asp. As such, no new matter has been added.

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[1] M.P.E.P. § 2422, Table 1 cites to the WIPO Standard ST.25 (1998), Appendix 2, Table 1, providing that the bases of a nucleotide sequence should be represented using the following one-letter code for nucleotide sequence characters, and defining that the symbol Y means either t/u or c with its origin of designation being a pyrimidine.

Rejection Under 35 U.S.C. § 112 Second Paragraph

The rejection of claim 4 under 35 U.S.C. § 112, second paragraph for being indefinite for failing to particularly point out and distinctly claim the subject matter is respectfully traversed in view of the above amendments.

According to the Examiner a polypeptide encoded by "a nucleotide sequence capable of hybridizing to full-length SEQ ID NO: 5" is ambiguous because the translation of the complementary sequence of a nucleic acid sequence of SEQ ID NO:5 would not encode WARP.

Claim 4 has been amended and now refers only to hybridzation to the complement of SEQ ID NO:5. Since a nucleotide sequence which hybridizes to the complement of SEQ ID NO:5 would encode WARP, claim 4 now particularly points out and distinctly claims the subject matter. Applicants respectfully request that this rejection be withdrawn.

Rejection Under 35 U.S.C. § 112 First Paragraph

The rejection of claim 4-5 and 43-44 under 35 U.S.C. § 112, first paragraph for failing to comply with the written description because new matter was introduced, is respectfully traversed in view of the amendments to the specification.

The substitute sequence listing filed on October 31, 2007 corrected the missing codon error in SEQ ID NO:5, as identified by the Examiner in the March 31, 2006 office action. Codon GAY, at nucleotide position 631 in SEQ ID NO: 5 now corresponds to amino acid Asp at position 211 in SEQ ID NO: 6. Support for this correction is found at paragraph [0071] of the originally filed specification as discussed above. Since no new matter has been introduced, this rejection should be withdrawn.

The rejection of claim 4, 12, and 43-44 under 35 U.S.C. § 112, first paragraph for failing to comply with the written description, is respectfully traversed.

According to the Examiner, Applicant was not in possession of the claimed invention because the specification failed to disclose the correct DNA coding sequence. This

rejection is respectfully traversed, because, as set forth above, SEQ ID NO:5 as originally filed has been corrected and this correction does not constitute new matter.

In addition, the Examiner argues that Applicants do not describe the invention of claims 4, 12, and 43-44 sufficiently to show possession of the claimed genus of polypeptides. According to the Examiner, the specification does not disclose sequences of 95% and 99% homology to SEQ ID NO:5 nor provide any suggestion as to how such sequences could be made or otherwise obtained other than by trial-and-error research. Applicants respectfully disagree and submit that written descriptive support is provided at paragraph [0043] which provides that 95% or 99% identity is preferable.

Also, the claimed genus is satisfied because as amended, claims 4 and 43 (and dependant claims 5 and 44) now recite a polypeptide which specifically binds to an antibody directed toward a von Willebrand Factor type A domain. The claims as amended now relate the structure of SEQ ID NO:5 with its function. The specification supports this amendment by describing the production of an anti-WARP antibody in Example 5, where the antibody specifically binds to the VA region of the WARP protein. In addition claim 31 as originally filed was directed to an isolated antibody specific for a polypeptide encoded by a nucleotide sequence, one of which is SEQ ID NO:5. Further, paragraphs [0088], [0090], and [0091] describe embodiments in which antibodies can be generated and used to bind to a region of the WARP protein. Therefore, any isolated polypeptide encoded by SEQ ID NO:5 or a nucleic acid which hybridizes to it and which also specifically binds an antibody targeted to a critical region of the WARP protein is likely to share a function of the WARP protein itself.

In addition, in the present specification Applicants have identified important WARP structural domains related to function. *See* Figure 1A showing the nucleotide and amino acid sequence of mouse WARP, Figure 1B showing the modular structure of WARP to represent conserved ECM protein modules, Figure 1C showing the alignment of mouse and human WARP amino acid sequences identifying important functional domains, and Example 11, paragraphs [0143] and [0144].

Further, the present application links structure to function by describing important functional domains in the WARP protein sequence for glycosylation, disulfide bond formation,

and ion binding. In identifying the human WARP by searching the genomic database with the mouse WARP protein sequence, Applicants disclose important homologous WARP domain regions in paragraph [0143]. Both the human and mouse homologs contain an 18 amino acid signal sequence with a cleavage site between Ala^{18} and Arg^{19}. The signal sequence was followed by a VA-domain of approximately 200 amino acids with a putative MIDAS motif and three potential O-linked sites at Ser^{148}, Thr^{362}, and Thr^{401}. Paragraph [0005] on page 4 states that the MIDAS motif bind divalent cations and gives I domains of integrins their adhesive and ligand binding properties (Lee *et al.,* 1995). Paragraph [0006] states that VA domains appear to play an important role in protein-protein interactions. Paragraph [0143] goes on to describe two conserved fibronectin type III (F3) repeats of approximately 80 amino acids in length, adjacent to the VA-domain, each containing a potential N-linked glycosylation site at Asn^{264} and Asn^{359} that fits the consensus sequence NxS/T. In addition, the C-terminus at the end of the second F3 repeat of 21 amino acids in length (24 in the human sequence) is rich in proline and arginine residues, and *did not show homology to any other protein by extensive database searching* (emphasis added), suggesting that this repeat is specific to WARP. The domain structure of WARP proteins is shown in Figure 1B.

In addition, alignment of the amino acid sequences of the human and mouse WARP protein show conserved sequences at the predicted N-terminal signal sequence, and at the position of potential N-linked and O-linked glycosylation sites. The conserved C-terminal cysteine residue (Cys^{393}) available for disulfide bond formation is shown boxed. *See* Figure 1C. Paragraph [0007] on page 5 refers to WARP as a novel disulfide-bonded oligomeric ECM glycoprotein, suggesting the functional importance of the disulfide bond.

Further, Example 11 again identifies that the amino acids within the MIDAS motif are critical for ion binding in both the mouse and human WARP, and that the overall arrangement of alpha helices and beta sheets which form the important secondary structural framework shared between all VA-like domains is conserved in WARP. (Page 54, paragraph [0144]). Also, Figure 2B shows that two F3 repeats are less conserved than the VA-domain, but the overall framework of 7 hydrophobic strands that form the β-sandwich typical of F3 repeats is conserved. Id. Although these studies used the mouse WARP protein, results are equally

applicable to the human WARP because these domains are conserved. Therefore, although all conservative amino acid substitutions in these domains will not necessarily result in a protein having WARP activity, those of ordinary skill in the art would expect that many of these conservative substitutions would result in a protein having the required activity. Further, amino acid substitutions outside of the two identified functional domains are unlikely to greatly affect activity of the protein. Thus, a correlation exists between the function of WARP and the structure of SEQ ID NO:5. Consequently, Applicants have provided information about which nucleic acids can vary from SEQ ID NO:5 in the claimed genus of nucleic acids and still encode a polypeptide having activity of the WARP protein.

Further, with the aid of a computer, one could list all the nucleic acid sequences that encode a polypeptide with 95% and 99% sequence identity to SEQ ID NO:5. Additionally, the level of skill and knowledge in the art is such that one of ordinary skill would be able to use conventional sequencing and nucleic acid synthesis techniques to routinely generate and identify nucleic acids that encode the polypeptide of SEQ ID NO:5, as well as those that encode any polypeptide having 95% and 99% structural similarity to SEQ ID NO:5. Thus, one of ordinary skill in the art could conclude that the Applicant had in possession of the claimed genus at the time of filing. In light of the preceding arguments, Applicants request that this rejection be withdrawn.

Rejection Under 35 U.S.C. § 112 First Paragraph

The rejection of claims 4, 12, 43-44 under 35 U.S.C. § 112, first paragraph for lack of enablement is respectfully traversed in view of the above amendments.

According to the Examiner, the fact that two nucleic acid sequences will hybridize under stringent conditions does not in and of itself require that the two sequences share any functional activity, and that it is unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences. Applicants respectfully disagree.

The present application links structure to function by describing important structural domains in the WARP protein sequence, as such, one skilled in the art would be able to use identify a functional WARP protein by looking for these domains, as discussed above.

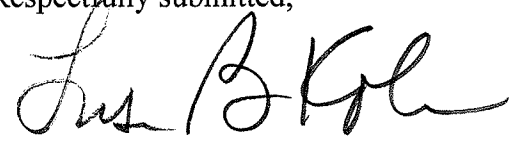
The Examiner concedes on page 4, bottom paragraph, of the present office action that "in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein." The present claims are therefore enabled because Applicants have defined important conserved domains of the WARP protein which one skilled in the art may depend on to assess the function of the isolated polypeptide claimed in the present invention. Applicants have also amended the claims to link the structure of the claimed polypeptide to its function. Based on the preceding argument, Applicants request that the present rejection be withdrawn.

Conclusion

Based on the above remarks and amendments, Applicants respectfully request a finding of allowance of claims 4, 5, 12 and 43-44. If the United States Patent and Trademark Office deems that an interview is appropriate, Applicants would appreciate the opportunity for such an interview. The Examiner is invited to contact the undersigned to discuss any outstanding matters that may be resolved by telephone.

In addition to the fee for the three-month extension of time to file this response, and the fee for the request for continued examination, Applicants believe that no additional fees are required. Should addition fees be required, or if fees are overpaid, the Director is hereby authorized to charge any required fees or credit any overpayments to Deposit Account 02-4377 of Baker Botts, LLP.

Respectfully submitted,



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